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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NICHOLS, CHRISTOPHER J	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,576	ERIKSSON, PETER	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-51 and 53-59* is/are pending in the application.

4a) Of the above claim(s) *32-41,43-51 and 54-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,53 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *32-51 and 53-59* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 July 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with **traverse** of Group III (claims 42, 52 now replaced by claim 59, and 53) in Paper No. 9 (13 March 2003) drawn to methods of propagating cells, stem cells, and/or cells derived from said cells by administration of a growth hormone or analogue *in vitro*, simultaneously administering a growth hormone or analogue to a patient, and then transplanting said cells into said patient is acknowledged. The traversal is on the ground(s) that all the claims could be conveniently prosecuted in the same application despite the different classification areas of the Groups. This is not found persuasive because each Group set forth in the previous Office Action (Paper No. 7, 19 September 2002) represents a patently distinct and independent invention. Group I requires search and consideration of growth hormone treatment, which is not required by Groups II and III. Group II requires search and consideration of growth hormone inhibition as treatment, which is not required by Groups I and III. Group III requires search and consideration of *ex vivo* transplantation therapy, which is not required by Groups I and II. Claims **32-41, 43-51,** and **54-58** are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9. The requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, and/or Claims

2. The Preliminary Amendments of Paper No. 5 (13 July 2001) and Paper No. 9 (13 March 2003) have been received and entered in full. Claims 1-31 have been canceled, claims 32-59 have been added, and claims 42, 53, and 59 are under examination.

Oath/Declaration

3. Receipt is acknowledged of papers filed under 35 U.S.C. 119 (a)-(d) based on an application filed in Sweden (9804064-5) on 25 November 1998. The Applicant has indicted that foreign priority is not claimed to the aforementioned application by checking "x No" underneath "PRIORITY CLAIMED UNDER 35 U.S.C. § 119" on the Oath/Declaration.

Drawings

4. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: "■" and "□". A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

5. Claim **53** is objected to because of the following informalities: claim 53 depends from claim 52, a canceled claim. In the interest of compact prosecution, the Examiner will consider claim 53 as dependent from claim 59 as the Applicant indicated that claim 59 replaced claim 52 (Paper No. 9, 13 March 2003). Regardless, appropriate correction of claim 53 is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims **42** is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a method or propagating progenitor cells, stem cells, and/or cells derived from said cells by administration of an effective amount of growth hormone in vitro*, does not reasonably provide enablement for *use of a "functionally equivalent analogue"*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

7. The above invention is drawn to a method of propagating progenitor cells, stem cells, and/or cells derived from said cells in vitro using growth hormone or a functionally equivalent analogue. The language of said claims encompasses a large range of growth factors and organic compounds.

8. The specification teaches that progenitor cells, stem cells, and/or cells derived from said cells can be cultured in the presence of growth hormone.

9. Since the specification fails to provide any guidance for the successful functionally equivalent analogues of growth hormone, and since resolution of the various complications in regards to the effects of any given analogue of a hormone is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention

as claimed would require the *de novo* determination of formulations with known analogues. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed method of propagation, such a disclosure would not be considered enabling since the state of stem and progenitor cells is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

10. The following references are cited herein to illustrate the state of the art of stem and progenitor cells.

11. Concerning the predictability of culturing neuronal stem cells, US 6284539 B1 (4 September 2001) Bowen & Johe discuss the varying results of culturing neuronal stem and progenitor cells in the presence of bFGF, EGF, and/or BDNF, all three of which fit under the rubric of "functionally equivalent analogues" of growth hormone (Col. 1-7) and conclude that:

> "Results such as these illustrate that identifying CNS stem cells, defining conditions that stably maintain CNS stem cell properties for long-term, and controlling their differentiation into mature cell types are neither obvious nor predictable to those skilled in the art." (Col. 7 lines 54-59)

12. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in*

vitro experiments to the *in vivo* diagnosis or risk assessment of stroke as exemplified in the reference above.

13. Claims **53** and **59** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

14. The above invention is drawn to a method of administering growth hormone or a functionally equivalent analogue to a patient, removing brain cells from said patient, culturing said brain cells *in vitro* and then transplanting the treated brain cells into said patient (an "*ex vivo*" therapy). The language of said claims encompasses both the removal of a small amount of brain cells and all stem or progenitor cells in the central or peripheral nervous system of the patient. Also, the invention covers all functionally equivalent analogues of growth hormone.

15. The specification teaches that growth hormone can be administered in conjunction with cortisol and L-thyroxine to hypophysectomized rats. The treatment of the hypophysectomized rats with the composition of growth hormone, cortisol, and L- thyroxine results an increased cell numbers in the granule cell layer, the subgranular layer, and hilus in said treated rats (Figures 1 and 2). The specification also teaches that the growth hormone, cortisol, and L-thyroxine treatment had a salubrious effect on the hypophysectomized rats as measured using a water maze test (Figure 3). Since the specification fails to provide any guidance for the successful showing that the growth hormone treatment actually induced linage determination or neurogenesis. Incorporation of BrdU is a non-specific test of cell proliferation and as such the data as filed

could be due to cell proliferation of glia such as microglia, astrocytes, oligodendrocytes and not neurons *per se*. In addition, since resolution of the various complications in regards to targeting neuronal populations *in vivo* is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of documented neurogenesis following growth hormone treatment. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

16. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of using stem or progenitor cells treated *in vitro* with growth hormone for transplant into a patient. Additionally, a person skilled in the art would recognize that predicting the efficacy of using growth hormone on stem or progenitor cells in a patient based solely on its performance *in vitro* is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods transplant methods, such a disclosure would not be considered enabling since the state of stem and progenitor cells is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

17. The following references are cited herein to illustrate the state of the art of *ex vivo* neuronal cell transplant technology.

18. Concerning the breadth of the claims, Rossi and Cattaneo (May 2002) "Neural stem cell therapy for neurological diseases: dreams and reality." Nature Reviews **3**: 401-409 teach that numerous obstacles exist to successful stem cell therapy and discuss the unpredictability of the fate of neural stem cells transplanted into a patient (Box 1). Furthermore adult stem cells are known to reside in the subventricular zone, hippocampus, and spinal cord (Figure 3). As noted above, the question remains for the skilled artisan as to how stem cells can be successfully removed from a patient without doing harm to said patient.

19. On the nature of the invention, Ellis *et al.* (December 1992) "A further British case of growth hormone induced Creutzfeldt-Jakob disease." Journal of Neurology, Neurosurgery, and Psychiatry **55**(12): 1200-1202 teaches that the administration of human growth hormone (GH) harvested from cadavers can transmit Creutzfeldt-Jakob disease the patient to which it is given (pp. 1200). While the Examiner understands that growth hormone is usually procured from recombinant sources or is chemically synthesized, the claims as written broadly read on all three groups; recombinantly produced, chemically synthesized, and GH harvested from human cadavers.

20. In view of predictability of the art of neuronal cell transplantation, Fricker-Gates *et al.* (2001) "Neural transplantation: Restoring complex circuitry in the striatum." Restorative Neurology and Neuroscience **19**(1-2): 119-138 teaches that transplantation of neural cells is not

sufficient to provide relief from disease and injury. Further issues, such as restoration of circuitry, integration into existing structures, and repair/replacement of loss neuronal function must be taken into consideration and thus add to the complexity and unpredictability of practicing the invention (pp. 131-132).

21. In further view of the predictability of the art of neuronal cell transplantation, US 5762926 (9 June 1998) Gage *et al.* teaches that the following factors are critical for reliable and effective cell transplantation: (1) Age of the donor, (2) Age of the host, (3) Availability of neurotrophic factors in the host and donor tissue, (4) Immunological response, (5) Target-donor matching, (6) Vascularization (Col. 2).

22. Taking these references into account, the invention as claimed does not provide sufficient guidance to overcome these obstacles or counteract the level of unpredictability in the art of neuronal cell transplantation. Furthermore, one skilled in the art would not accept on the removal of an unspecified amount of brain cells from a patient. The skilled artisan would expect most, if not all, of such procedures to be injurious or fatal to a patient. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of removing brain cells from a patient. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with brain surgery and specifically regarding the instant methods claimed.

23. Claims **53** and **59** are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the

elements. See MPEP § 2172.01. The omitted elements are: the reason for transplanting cells into a patient and where the transplant is to occur.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

24. Claims **42, 53,** and **59** are rejected under 35 U.S.C. 102(a) as being anticipated by the published patent application Sweden (9804064-5) A+ Science Invest AB (25 November 1998). 9804064-5 teaches a method of inducing lineage determination, propagating and/or inducing or maintaining the genesis of neurons, oligodendrocytes, astroglial cells from progenitor cells, stem cells, and/or cells derived from said cells by administration of an effective amount of growth hormone or a functionally equivalent analogue thereof to stem cells, progenitor cells, neurons, astroglial cells and/or oligodendrocytes in vitro thus meeting the limitations of claims 42, 53, and 59 (pp. 16; claim 16).

25. Claim **42** is rejected under 35 U.S.C. 102(b) as being anticipated by Almazan *et al.* (August 1985) "Epidermal Growth Factor and Bovine Growth Hormone Stimulate Differentiation and Myelination of Brain Cell Aggregates in Culture." Developmental Brain Research **353**(2): 257-264. Almazan *et al.* (1985) teaches a method of growing fetal cells derived

from the telencephalon of rats in the presence of bovine growth hormone thus meeting the limitations of claim 42 (pp. 258).

26. Claim **42** is rejected under 35 U.S.C. 102(b) as being anticipated by US 5750376 (12 May 1998) Weiss *et al.* US 5750376 discloses an *in vitro* method for proliferation and differentiation of neural stem cells and stem cell progeny comprising the steps of (a) isolating the cell from a mammal, (b) exposing the cell to a culture medium containing a growth factor, (c) inducing the cell to proliferate, and (d) inducing the cell to differentiate thus meeting the limitations of claim 42 (Col. 10 lines 58-65; Col. 11 lines 1-5). US 5750376 also discloses that the growth factor including in said culture medium is growth hormone thus meeting the limitations of claim 42 (Col. 20 lines 40-56). US 5750376 also teaches that said method can be practiced with stem cells, progenitor cells, and their progeny thus meeting the limitations of claim 42 (Col. 12 lines 40-65).

Summary

27. Claims 42, 53, and 59 are hereby rejected.

28. The following articles and patents were found by the Examiner during the art search and is here made of note:

a. US 5851832 (22 December 1998) Weiss *et al.*

b. US 5980885 (9 November 1999) Weiss *et al.*

c. Ajo *et al.* (2003) "Growth Hormone Action on Proliferation and Differentiation of Cerebral Cortical Cells from Fetal Rat." Endocrinology **144**(3): 1086-1097.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

CJN
June 3, 2003